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Gemcitabine Plus Carboplatin Compared With Carboplatin in Patients With Platinum-Sensitive Recurrent Ovarian Cancer: An Intergroup Trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
Most patients with advanced ovarian cancer develop recurrent disease. For those patients who recur at least 6 months after initial therapy, paclitaxel platinum has shown a modest survival advantage over platinum without paclitaxel; however, many patients develop clinically relevant neurotoxicity, frequently resulting in treatment discontinuation. Thus, an alternative regimen without significant neurotoxicity was evaluated by comparing gemcitabine plus carboplatin with single-agent carboplatin in platinum-sensitive recurrent ovarian cancer patients.

Methods
Patients with platinum-sensitive recurrent ovarian cancer were randomly assigned to receive either gemcitabine plus carboplatin or carboplatin alone, every 21 days. The primary objective was to compare progression-free survival (PFS).

Results
Three hundred fifty-six patients (178 gemcitabine plus carboplatin; 178 carboplatin) were randomly assigned. Patients received a median of six cycles in both arms. With a median follow-up of 17 months, median PFS was 8.6 months (95% CI, 7.9 to 9.7 months) for gemcitabine plus carboplatin and 5.8 months (95% CI, 5.2 to 7.1 months) for carboplatin. The hazard ration (HR) for PFS was 0.72 (95% CI, 0.58 to 0.90; $P = .0031$). Response rate was 47.2% (95% CI, 39.9% to 54.5%) for gemcitabine plus carboplatin and 30.9% (95% CI, 24.1% to 37.7%) for carboplatin ($P = .0016$). The HR for overall survival was 0.96 (95% CI, 0.75 to1.23; $P = .7349$). While myelosuppression was significantly more common in the combination, sequelae such as febrile neutropenia or infections were uncommon. No statistically significant differences in quality of life scores between arms were noted.

Conclusion
Gemcitabine plus carboplatin significantly improves PFS and response rate without worsening quality of life for patients with platinum-sensitive recurrent ovarian cancer.

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INTRODUCTION

Despite progress in the first-line treatment of ovarian cancer, the majority of patients relapse and die within 5 years.[1,2] Retrospective studies of platinum-based, second-line therapies have led to the identification of two subgroups of patients with recurrent ovarian cancer: those with so-called platinum-resistant disease and those with platinum-sensitive disease.[3,4] Platinum-sensitive disease is characterized by a response to first-line platinum-based therapy and a relapse-free period of at least 6 months after the last platinum treatment. Retreatment with a single-agent platinum has long been considered to be standard therapy for these patients, and based on its favorable therapeutic profile, carboplatin has become the agent of choice.

In a recently published pooled analysis of three randomized phase III trials, the Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and International Collaborative Ovarian Neoplasm (ICON) collaborators demonstrated that, compared with conventional platinum-based therapies, paclitaxel plus platinum yielded significant improvements

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in progression-free survival (hazard ratio [HR], 0.76; 95% CI, 0.66 to 0.89; $P = .0004$) and overall survival (HR, 0.82; 95% CI, 0.69 to 0.97; $P = .02$) in patients with platinum-sensitive recurrent ovarian cancer.[5] Global quality of life did not differ significantly between the arms, but 20% of patients receiving paclitaxel platinum reported grade 2 to 4 neurotoxicity compared with 1% receiving conventional platinum therapy. Because many patients in that study did not receive paclitaxel as first-line treatment, these neurotoxicity figures with second-line paclitaxel platinum might underestimate the true incidence. In fact, OVAR 2.2, the AGO-OVAR part of the ICON4 study, was discontinued early after slow recruitment due to the investigators' concern that retreatment with paclitaxel would lead to an excess of neurotoxicity after first-line platinum paclitaxel, and a considerable proportion of otherwise eligible patients could not be entered at recurrence because of persistent neurotoxicity from their first-line therapy.

In general, ovarian cancer patients relapsing after first-line platinum paclitaxel therapy are at risk for significant neurotoxicity when retreated with the same regimen due to the cumulative neurotoxicity of both platinum and paclitaxel.[6] When administered in the first-line setting in a recent AGO-OVAR study, paclitaxel with carboplatin or cisplatin was associated with grade 1 to 4 neurotoxicity in the majority of patients (75% and 83%, respectively).[1] In the same study, neurotoxicity slowly resolved after therapy discontinuation, but it also persisted in 20% of patients for 2 years or longer. Thus, although the efficacy of platinum paclitaxel readministration appears promising for platinum-sensitive ovarian cancer patients, the frequency of clinically significant residual neurotoxicity after first-line treatment underscores the need for an active platinum-based combination therapy that is not associated with this toxic effect.

The nucleoside analog gemcitabine has shown promising single-agent activity in phase II studies of recurrent ovarian cancer, including patients with prior platinum and/or taxane exposure.[7-9] Thus, the AGO-OVAR investigators conducted a phase I/II study of gemcitabine plus carboplatin in patients with platinum-sensitive recurrent ovarian cancer to determine recommended doses to give in combination and to provide some preliminary information on efficacy.[10] Results showed a high response rate (62.5%) and encouraging progression-free and overall survival with acceptable toxicity.

Based on the considerations herein, a randomized phase III study was initiated to compare the efficacy of gemcitabine plus carboplatin with carboplatin alone in patients with platinum-sensitive recurrent ovarian cancer. The primary objective was to compare progression-free survival between treatment arms. Secondary objectives included comparisons of response rate, duration of response, overall survival, quality of life, and toxicity. Important parts of this final analysis have been presented at the 40th Annual Meeting of the American Society of Clinical Oncology in 2004 and the 10th Biennial Meeting of the International Gynecologic Cancer Society in 2004.[11,12]

METHODS

Patients

Women at least 18-years-old with recurrent ovarian cancer at least 6 months after completion of first-line, platinum-based therapy were eligible. In addition, patients were required to have measurable or assessable lesions per Southwest Oncology Group criteria,[13] an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate bone marrow reserve (absolute neutrophil count [ANC] $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L), an estimated glomerular filtration rate (GFR) greater than 50 mL/min, no serious

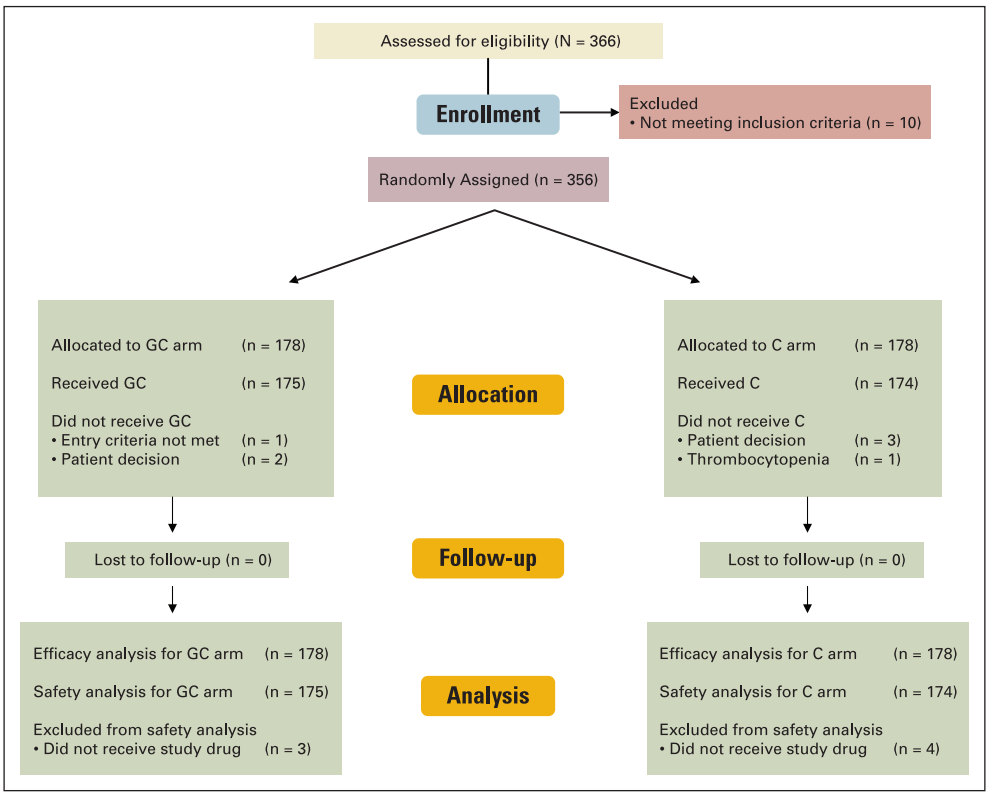

Fig 1. Trial profile. GC, gemcitabine and carboplatin; C, carboplatin.

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concomitant systemic disorders incompatible with the study, and an estimated life expectancy 12 weeks or longer. Written informed consent was obtained from all patients before enrollment. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Before patient entry, the appropriate institutional ethics committee for each participating institution approved the protocol.

Procedures

This trial was an international, open-label, randomized, phase III study of the Gynecologic Cancer Intergroup conducted by the AGO-OVAR, National Cancer Institute of Canada Clinical Trials Group, and European Organisation for Research and Treatment of Cancer (EORTC) Gynecologic Cancer Group. Before random assignment through the central AGO-OVAR office, the enrolling investigator stratified the patients according to platinum-free interval (6 to 12 months *v* ≥ 12 months), first-line therapy (platinum paclitaxel *v* other platinum-based therapy), and bidimensionally measurable disease (yes *v* no). A 1:1 random assignment was used within each stratum with a block size of 10; each patient had a 50% chance of random assignment to either treatment arm.

Patients in the experimental arm received gemcitabine 1,000 mg/m^2 on days 1 and 8 and carboplatin area under the curve (AUC) 4 mg/mL/min on day 1.[10] Patients in the control arm received carboplatin AUC 5 on day 1, based on the Calvert formula.[14] The AUC calculation was based on GFR calculation according to the formula of Jelliffe.[15] Cycles were repeated every 21 days for six cycles in the absence of progressive disease or unacceptable toxicity. At the investigator's discretion, benefiting patients could receive a maximum of 10 cycles of therapy.

Cycles could be postponed up to 2 weeks due to toxicity, and longer toxicity-related delays led to treatment discontinuation. Treatment resumed after recovery from nonhematologic and hematologic toxicities (ANC ≥ 1.5 $\times 10^9$/L and platelets ≥ 100 $\times 10^9$/L). In the gemcitabine plus carboplatin arm, day 8

Table 1. Baseline Patient Characteristics

Characteristic	Arm: Gemcitabine and Carboplatin No.	Arm: Gemcitabine and Carboplatin %	Arm: Carboplatin No.	Arm: Carboplatin %	Total No.	Total %
No. of patients randomly assigned	178	100.0	178	100.0	356	100.0
Age, years						
Median	59		58		58	
Range	36-78		21-81		21-81	
Ethnicity						
Western Asian	34	19.1	37	20.8	71	19.9
White	127	71.3	126	70.8	253	71.1
East/Southeast Asian	12	6.7	12	6.7	24	6.7
Hispanic	2	1.1	3	1.7	5	1.4
Other	3	1.7	0	0.0	3	0.8
FIGO stage at initial diagnosis						
Ia-IIa	16	9.0	14	7.9	30	8.4
IIb-IIIa	22	12.4	12	6.7	34	9.6
IIIb	16	9.0	22	12.4	38	10.7
IIIc	97	54.5	107	60.1	204	57.3
IV	27	15.2	22	12.4	49	13.8
Unspecified	0	0.0	1	0.6	1	0.3
ECOG performance status						
ND	5	2.8	4	2.2	9	2.5
0	83	46.6	93	52.2	176	49.4
1	79	44.4	72	40.4	151	42.4
2	11	6.2	9	5.1	20	5.6
Differentiation						
Well differentiated	15	8.4	13	7.3	28	7.9
Moderately differentiated	51	28.7	49	27.5	100	28.1
Poorly differentiated	78	43.8	88	49.4	166	46.6
Undifferentiated	10	5.6	7	3.9	17	4.8
Unknown	24	13.5	21	11.8	45	12.6
Prior therapy						
Surgery	178	100.0	178	100.0	356	100.0
Radiotherapy	4	2.2	3	1.7	7	2.0
Platinum based + taxane*	125	70.2	127	71.3	252	70.8
Immunotherapy	4	2.2	4	2.2	8	2.2
Hormonal therapy	6	3.4	2	1.1	8	2.2
Platinum-free interval, months						
< 6	1	0.6	0	0.0	1	0.3
6-12	71	39.9	71	39.9	142	39.9
>12	106	59.6	107	60.1	213	59.8

Abbreviations: FIGO, International Federation of Oncology and Obstetrics; ECOG, Eastern Cooperative Oncology Group; ND, not determined.
*1.7% (n = 3) of patients in the gemcitabine-carboplatin arm and 3.9% (n = 7) in the carboplatin arm received prior docetaxel combination therapy.

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Table 2. Dose Administration

Parameter	Gemcitabine and Carboplatin Arm (n = 178)				Carboplatin Arm (n = 178)		
	Gemcitabine		Carboplatin		Carboplatin		
	No.	%	No.	%	No.	%	P*
Cycles							
Median/patient completed	6				6		
Range	0-10				0-9		
Total completed	961				888		
Delayed	314	32.7			236	26.6	.0044
Doses							
Planned†	1,928		965		897		
Reduced	200	10.4	17	1.8	34	3.8	.0099‡
Omitted	265	13.7	2	0.2	NA§		NA
Dose intensity							
Planned mean dose, per week	666.7 mg/m^2		AUC 1.33		AUC 1.67		
Actual mean dose	504.2 mg/m^2		AUC 1.28		AUC 1.64		
Relative dose intensity (actual/planned ×100%)	75.6		96.2		98.2		

Abbreviations: AUC, area under curve; NA, not applicable.
*Significance at $P < .05$, using Fisher's exact test.
†Number of doses per protocol while the patient was on study and receiving treatment.
‡Comparing carboplatin treatments.
§A cycle only started with dose administration.

gemcitabine was reduced 50% if ANC ≥1.0 to 1.4 ×10^9/L and/or platelets 75 to 99 ×10^9/L, and it was omitted if below these values. For grade 3 nonhematologic toxicities (excluding nausea/vomiting), dose modifications and/or study discontinuation were at the investigator's discretion. Successive reductions by one dose level were required for treatment delays 1 week or longer due to toxicity, ANC less than 0.5 ×10^9/L for more than 5 days (or < 0.1 ×10^9/L for > 3 days), febrile neutropenia, platelets less than 25 ×10^9/L, and grade 3/4 nonhematologic toxicities (except nausea/vomiting). For the gemcitabine plus carboplatin arm, dose level −1 was gemcitabine 800 mg/m^2, and dose level −2 was omission of day 8 gemcitabine; carboplatin was not reduced in this arm. For the carboplatin arm, dose level −1 was a reduction to AUC 4; if additional dose reductions were required, patients were discontinued.

Patients were assessed before random assignment, before every cycle during treatment, and every 2 to 3 months after treatment for at least 2 years. The baseline assessment included medical history, physical examination, blood counts and chemistries, and radiologic studies to establish extent of tumor burden. Within 2 weeks before enrollment and before every cycle, quality of life was assessed using the EORTC Quality of Life Questionnaires QLQ-C30 and QLQ-OV28, version 2.[16,17] Toxicity was assessed every cycle and 30 days after the last treatment; blood counts were obtained on days 1 and 8 of each cycle.

Progression-free survival was defined as the time from the date of random assignment to the date of disease progression or death from any cause. Progressive disease was based on clinical and/or radiologic evaluation. Progressive disease was not based on CA-125 elevation without other clinical or radiologic evidence of disease progression. Duration of response was measured from the date of first response to the date of disease progression or death due to any cause. Overall survival was measured from the date of random assignment to the date of death from any cause.

All randomly assigned patients were eligible for efficacy evaluation based on an intent-to-treat analysis. Response was measured according to standard Southwest Oncology Group criteria.[13] Patients with quality of life data at baseline and postbaseline were included in the quality of life analyses, and changes were measured from baseline to treatment discontinuation between and within arms. All patients receiving at least one dose of study drug were included in the toxicity analysis, which was graded according to the National Cancer Institute Common Toxicity Criteria version 2.[18,19]

Statistical Analyses

The target enrollment was 350 patients. Three hundred fifty-six patients were randomly assigned onto this study. Based on historical data, it was expected that between 300 and 350 patients with disease progression would be observed. The expected median progression-free survival for carboplatin was 6 months; and based on the aforementioned AGO-OVAR phase I/II study[10] it was 8.5 months for gemcitabine plus carboplatin; thus, the constant HR was 0.71. Using a significance level of .05 and the constant HR of 0.71, the log-rank comparison of progression-free survival can identify a significant difference between regimens with 85% power.[20]

The study was not powered to detect differences in overall survival. In order to detect a 25% improvement in overall survival (that is assuming a HR of 0.80), the power would have been only 55% with an $\alpha = .05$ and 352 deaths.

For time-to-event parameters, Kaplan-Meier estimations were used and log-rank χ^2 tests compared the distribution between groups. For progression-free survival, separate univariate Cox models were fitted individually for each covariate. Factors that showed individual prognostic value ($P < .05$) were added to a model with treatment to assess the effect of treatment when adjusting for any significant univariate prognostic factors. Covariates included age (> 60 *v* ≤ 60), performance status (0 *v* 1-2), prior platinum therapy (platinum plus nonpaclitaxel *v* platinum plus paclitaxel), disease status (bidimensionally measurable *v* assessable), and duration of platinum-free interval (6 to 12 months *v* > 12 months). Response rates were compared using an unadjusted normal approximation for the difference of two binomial proportions, and 95% CIs were constructed. Changes in QLQ-C30 and QLQ-OV28 baseline scores were compared within and between arms using a paired *t*-test and an analysis of variance (ANOVA). All analyses were done with SAS version 8.2 (SAS Institute, Cary, NC).

Role of the Funding Source

This study was supported by Lilly Deutschland GmbH, Bad Homburg, Germany. It was designed by the study groups in accordance with Lilly Deutschland GmbH. The study was performed and analyzed independently by the study groups. All the groups, as well as the principal investigator, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

From September 1999 to April 2002, 366 patients were enrolled. Figure 1 shows the trial profile; 10 patients did not fully meet the

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eligibility criteria and were not randomly assigned. Seven randomly assigned patients did not receive study therapy due to patient decision, ineligibility, or thrombocytopenia. The treatment arms were well balanced for baseline patient and disease characteristics (Table 1).

Of the 1,849 total cycles administered, 961 cycles were in the gemcitabine plus carboplatin arm, and 888 cycles were in the carboplatin arm (Table 2). Patients in the gemcitabine plus carboplatin arm received 75.6% of the planned mean dose of gemcitabine (92.8% on day 1 and 63.4% on day 8) and 96.2% of the planned dose of carboplatin. Patients in the carboplatin arm received 98.2% of the planned dose.

Grade 3/4 hematologic toxicities were significantly more frequent in the gemcitabine plus carboplatin arm than the carboplatin arm; neutropenia was the predominant toxicity (Table 3). Although the use of granulocyte growth factors was significantly higher in the gemcitabine plus carboplatin arm (23.6%) than the carboplatin arm (10.1%), the frequency of febrile neutropenia and use of intravenous antibiotic treatment did not differ significantly between arms. Patients in the gemcitabine plus carboplatin arm received more RBC (27.0%) and platelet transfusions (8%) than those in the carboplatin arm (6.7% and 3%, respectively). Fewer than 8% of patients in either arm received erythropoietin for anemia. Few patients discontinued treatment due to hematologic events (such as complicated neutropenia or thrombocytopenia) in either arm (5.1% in the gemcitabine plus carboplatin arm; 4.0% in the carboplatin arm). The overall incidence of grade 3/4 nonhematologic toxicities was modest with less than 5% of patients on either arm having nausea, vomiting, motor or sensory neuropathy, or renal toxicity (Table 3). Of note, grade 2 alopecia was reported in 14.3% of gemcitabine plus carboplatin patients and 2.3% of carboplatin patients.

For the progression-free survival assessment, 325 events were observed. With a median follow-up of 17 months, the HR for progression-free survival was 0.72 (95% CI, 0.58 to 0.90; log-rank $P = .0031$), indicating a 28% reduction in the progression-free event rate. Median progression-free survival was 8.6 months (95% CI, 7.9 to 9.7 months) for the gemcitabine plus carboplatin arm and 5.8 months (95% CI, 5.2 to 7.1 months) for the carboplatin arm (Fig 2). Overall survival was assessed when 71% of the study population had died. The HR for overall survival was 0.96 (95% CI, 0.75 to 1.23; log-rank $P = .7349$). Median overall survival was 18.0 months (95% CI, 16.2 to 20.2 months) for the gemcitabine plus carboplatin arm and 17.3 months (95% CI, 15.2 to 19.3 months) for the carboplatin arm (Fig 3). Response rate was significantly higher in the gemcitabine plus carboplatin arm than the carboplatin arm (47.2% *v* 30.9%; $P = .0016$; Table

Table 3. Selected NCI-CTC Toxicities and Associated Supportive Care

	Arm																
	GC Arm (n = 175)								C Arm (n = 174)								
	Grade								Grade								
	1		2		3		4		1		2		3		4		
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P** for Grades 3 and 4	*P**
Hematologic																		
Anemia	32	18.3	73	41.7	39	22.3	9	5.1	71	40.8	44	25.3	10	5.7	4	2.3	< .001	
Neutropenia	9	5.1	27	15.4	73	41.7	50	28.6	44	25.3	33	19.0	19	10.9	2	1.1	< .001	
Thrombocytopenia	41	23.4	36	20.6	53	30.3	8	4.6	66	37.9	14	8.0	18	10.3	2	1.1	< .001	
Nonhematologic																		
Allergic reaction/ hypersensitivity	1	0.6	4	2.3	3	1.7	1	0.6	3	1.7	2	1.1	3	1.7	2	1.1	.7503	
Alopecia	61	34.9	25	14.3	NA	NA	NA	NA	27	15.5	4	2.3	NA	NA	NA	NA	NA†	
Diarrhea	16	9.1	7	4.0	3	1.7	0	0	7	4.0	6	3.4	0	0	0	0	.2479	
Dyspnea	1	0.6	12	6.9	2	1.1	0	0	2	1.1	4	2.3	2	1.1	1	0.6	.6848	
Fatigue	29	16.6	35	20.0	3	1.7	1	0.6	25	14.4	23	13.2	3	1.7	0	0	.99	
Febrile neutropenia	0	0	0	0	2	1.1	0	0	0	0	0	0	0	0	0	0	.4986	
Infection without neutropenia	1	0.6	1	0.6	0	0	1	0.6	1	0.6	1	0.6	0	0	0	0	.99	
Infection with neutropenia	1	0.6	0	0	0	0	0	0	0	0	1	0.6	0	0	0	0	NA	
Neuropathy, motor	9	5.1	1	0.6	1	0.6	0	0	6	3.4	1	0.6	0	0	0	0	.99	
Neuropathy, sensory	43	24.6	7	4.0	2	1.1	0	0	38	21.8	6	3.4	3	1.7	0	0	.6848	
Vomiting	41	23.4	28	16.0	5	2.9	0	0	32	18.4	23	13.2	2	1.1	1	0.6	.7234	

	GC Arm (n = 178)		C Arm (n = 178)		
Supportive Care	No.	%	No.	%	
Treatment					
Parenteral Antibiotics	15	8.4	9	5.1	.2905
G-CSF or GM-CSF	42	23.6	18	10.1	.0010
RBCs	48	27.0	12	6.7	< .001
EPO	13	7.3	7	3.9	.2493

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; EPO, erythropoietin or epoetin; NA, not applicable

*Significance at $P < .05$, comparing the two arms using Fisher's exact test.

†Not applicable, grade 3/4 alopecia are not recognized by NCI-CTC (version 2.0 and later).

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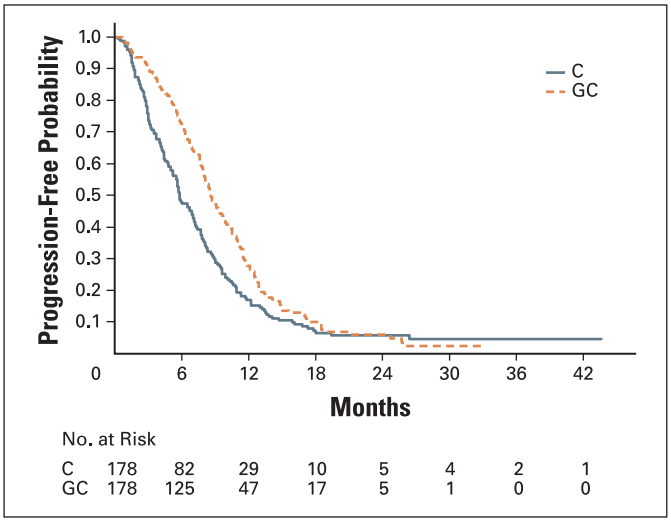

Fig 2. Kaplan-Meier estimates of progression-free survival. The hazard ratio for recurrence in the gemcitabine plus carboplatin arm, as compared with the carboplatin arm, was 0.72 (95% CI, 0.58 to 0.90; log-rank $P = .0031$). C, carboplatin; GC, gemcitabine and carboplatin.

Table 4. Response

Response	Arm: Gemcitabine and Carboplatin (n = 178) No.	%	Arm: Carboplatin (n = 178) No.	%
Not assessable/ not done	12	6.7	25	14.0
PD	14	7.9	29	16.3
SD	68	38.2	69	38.8
PR	58	32.6	44	24.7
CR	26	14.6	11	6.2
Overall response rate (CR + PR)	84	47.2*	55	30.9
95% CI		39.9 to 54.5		24.1 to 37.7

Abbreviations: PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.
*Significantly different between arms ($P = .0016$) based on calculation of an unadjusted normal approximation for the difference of two binomial proportions.

4). Median duration of response was 8.4 months (95% CI, 7.6 to 9.6 months) in the gemcitabine plus carboplatin arm and 7.3 months (95% CI, 5.9 to 8.2 months) in the carboplatin arm (log-rank $P = .2511$).

Employing the Cox proportional hazards model, a univariate analysis assessed the effect of prespecified prognostic factors on progression-free survival (Table 5). Platinum-free interval was an important prognostic factor individually ($P = .0015$). Adjusting the effect of this factor on treatment showed that the positive effect of gemcitabine plus carboplatin was maintained when adjusting for platinum-free interval (adjusted HR, 0.71; 95% CI, 0.57 to 0.88; Table 5).

To illustrate the effect of prespecified prognostic factors on progression-free survival, forest plots were constructed (Fig 4). Of note, improved progression-free survival was maintained in patients who received platinum-taxane therapy in the first-line setting and in patients whose platinum-free interval was less than 12 months.

A total of 152 patients (85.4%) in the gemcitabine plus carboplatin arm and 147 patients (826%) in the carboplatin arm completed a quality of life questionnaire at baseline and at least one postbaseline questionnaire. For all scales/items, there were no statistically significant treatment differences for baseline scores between arms, as well as

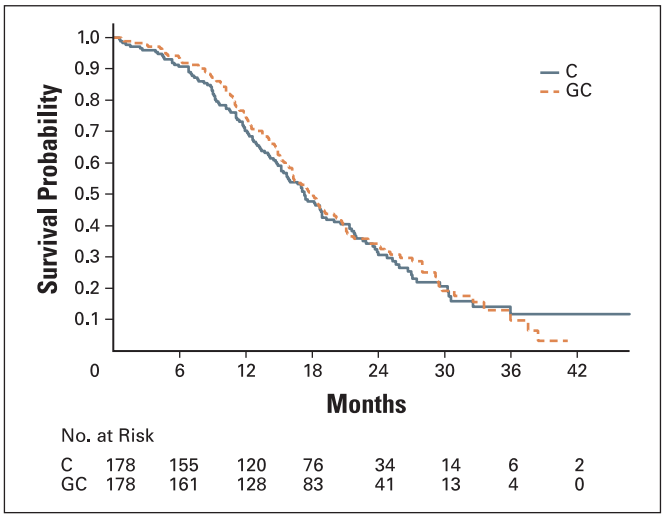

Fig 3. Kaplan-Meier estimates of overall survival. The hazard ratio for survival in the gemcitabine and carboplatin arm, as compared with the carboplatin arm, was 0.96 (95% CI, 0.75 to 1.23; $P = .7349$). The study was not powered to detect significant differences in overall survival. C, carboplatin; GC, gemcitabine and carboplatin.

Table 5. Univariate and Multivariate Analysis of Prognostic Factors Affecting Progression-Free Survival

Covariate	Progression-Free Survival HR	95% CI	Wald's P
Univariate analysis			
Age, years			.7528
60	1		
> 60	1.04	0.83 to 1.29	
ECOG performance status			.1994
0	1		
1 or 2	1.16	0.93 to 1.44	
Prior platinum therapy			.6575
Platinum + non-paclitaxel	1		
Platinum + paclitaxel	1.06	0.83 to 1.34	
Disease status			.4143
Assessable	1		
Bidimensionally measured	0.81	0.48 to 1.36	
Platinum-free interval, months			.0015
6-12	1		
> 12	0.70	0.56 to 0.87	
Actual therapy			.0032
Carboplatin arm	1		
Gemcitabine and carboplatin arm	0.72	0.58 to 0.90	
Multivariate analysis			
Actual therapy			.0019
Carboplatin arm	1		
Gemcitabine and carboplatin arm	0.71	0.57 to 0.88	
Platinum-free interval, months			.0010
6-12	1		
> 12	0.69	0.55 to 0.86	

Abbreviations: HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group.

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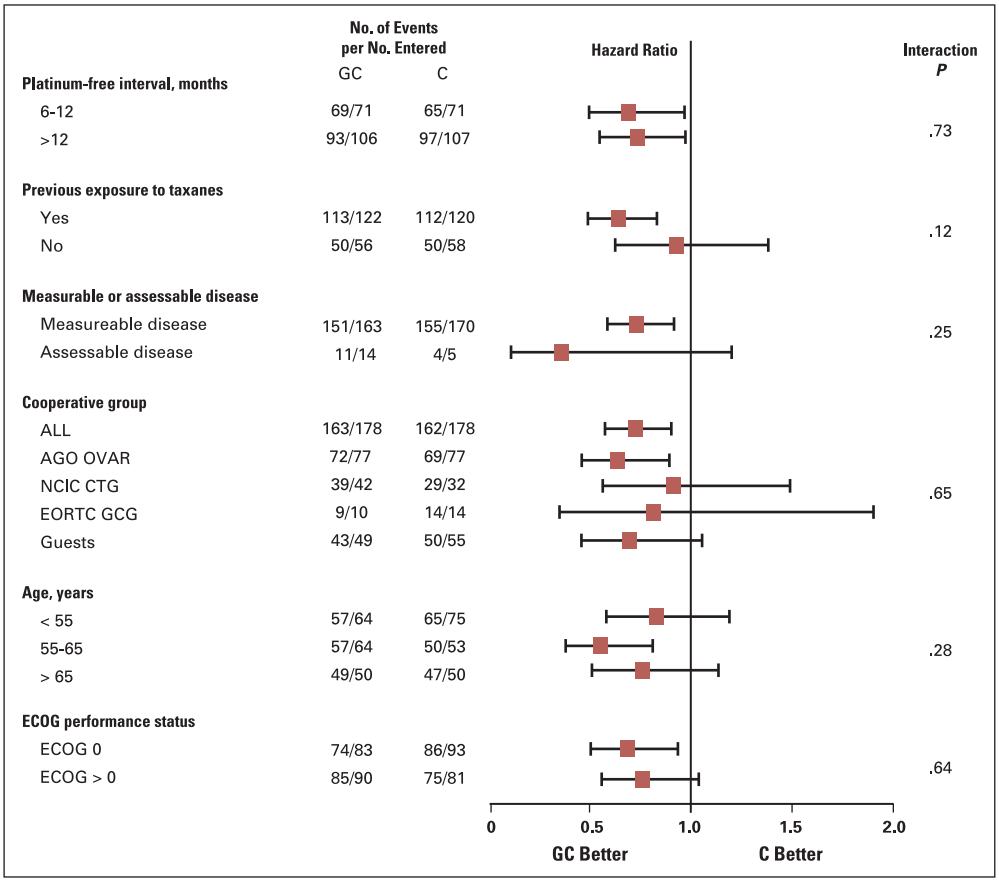

Fig 4. Subgroup analysis of progression-free survival. In measurable or assessable disease: one patient in GC arm and three patients in C arm had neither measurable nor assessable disease. GC, gemcitabine and carboplatin; C, carboplatin; AGO-OVAR, Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; EORTC GCG, European Organisation for Research and Treatment of Cancer Gynecologic Cancer Group; ECOG, Eastern Cooperative Oncology Group.

for score changes from baseline to treatment discontinuation between arms (Fig 5).

There were no major differences in postprogression therapy between treatment arms: 135 patients (75.8%) in the gemcitabine plus carboplatin arm received additional chemotherapy, compared with 129 patients (72.5%) in the carboplatin arm. Detailed information was available for 68 patients (38%) in the gemcitabine plus carboplatin arm and for 71 patients (40%) in the carboplatin arm. Twenty patients (29%) in the gemcitabine plus carboplatin arm versus 16 patients (23%) in the carboplatin arm received platinum again, 20 patients (29%) versus 15 patients (21%) received topotecan, 10 patients (15%) versus 13 patients (18%) received anthracyclines, eight patients (12%) versus three patients (4%) received etoposide, eight patients (12%) versus 14 patients (20%) received alkylating agents, one patient (1%) versus five patients (7%) received taxanes, and no patients (0%) versus four patients (6%) received gemcitabine, respectively.

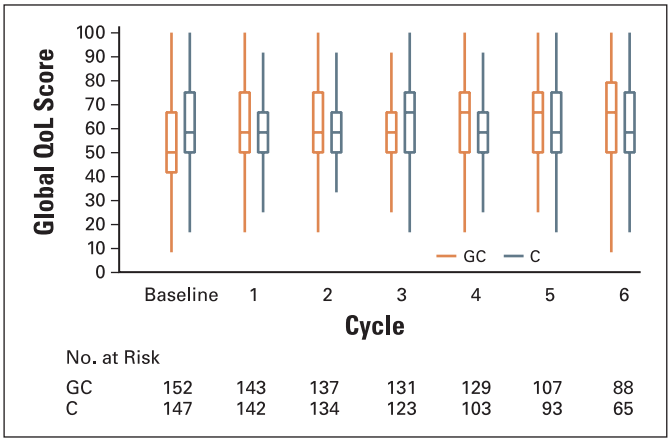

Fig 5. Global quality of life (QoL). Least square means of the global QoL scores for the randomly assigned patients (n = 152 for GC; n = 147 for C) are plotted. Scores range 0 to 100 (100 = best score). The bottom and top edges of the box are located at the sample 25th and 75th percentiles. The center horizontal line is drawn at the 50th percentile (or median). The vertical lines show the range of values. GC, gemcitabine and carboplatin; C, carboplatin.

DISCUSSION

As epithelial ovarian cancer has frequently followed a trajectory more like a chronic illness than an immediate life-threatening disease, the long-term treatment complications associated with improved survival are increasingly becoming clinically relevant. While platinum taxane-based regimens have improved the clinical outcome of ovarian cancer patients, their widespread use as first-line treatments and their cumulative neurotoxicity limit their utility for patients with recurrent ovarian cancer, the majority of whom are platinum sensitive at their first relapse.[1,2] Thus, there is an urgent need to identify new platinum-based combination therapies in platinum-sensitive recurrent ovarian cancer that prolong overall and progression-free survival and palliate cancer symptoms with acceptable toxicity and quality of life.

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This is the first randomized phase III study comparing gemcitabine plus carboplatin with carboplatin in platinum-sensitive recurrent ovarian cancer patients. This study demonstrates that the regimen of gemcitabine plus carboplatin is feasible and significantly increases progression-free survival and response rates in this patient population. In addition, based on the Cox model analysis, the treatment effect of gemcitabine plus carboplatin persisted even when adjusted for significant prognostic factors like prior taxane use and platinum-free interval. This is in accordance with the ICON4/AGO-OVAR 2.2 study, where progression-free survival was longer in patients treated with the combination carboplatin plus paclitaxel than in patients treated with carboplatin alone, irrespective of previous exposure to taxane and time since completion of last chemotherapy.[5]

This study did not show significant improvement in overall survival with gemcitabine plus carboplatin, but it was not designed and powered to do so. In trials of patients with advanced, incurable cancers, improvement in survival can be easily obscured by poststudy therapy on study discontinuation; furthermore, overall survival reflects all administered lines of therapy and not a specific regimen. The Third International Ovarian Cancer Consensus Conference of the Gynecologic Cancer Intergroup 2004 has stated that it is not possible to standardize treatment for recurrence in ovarian cancer patients, and that progression-free survival is an important end point for the management of ovarian cancer patients and for the assessment of new treatments.[21] In addition, there is evidence from other tumor types (for example, colon cancer) that progression-free and overall survival are highly correlated, both within patients and trials.[22] Therefore, progression-free survival is an adequate and clinically relevant end point in ovarian cancer trials.

While hematologic toxicity was significantly higher with gemcitabine plus carboplatin, the toxicity profile was acceptable, as the increased toxicity was associated with improved efficacy, infrequent clinically significant sequelae (for example, febrile neutropenia), and no diminution of quality of life. Despite that the majority of patients were previously exposed to platinum taxane regimens in the first-line setting, the incidence of significant neurotoxicity was low and comparable between arms. As platinum paclitaxel regimens are the cornerstone of first-line treatment of ovarian cancer, residual neurotoxicity and increased risk for neurotoxicity must be considered when selecting second-line therapy. The high frequency of neurotoxicity observed with paclitaxel-platinum therapy in the aforementioned ICON4/AGO-OVAR 2.2 study highlights the need to consider prior therapy and the efficacy and safety of new therapy when palliation for patients with incurable malignancies is required.

Of note, the treatment effect of gemcitabine plus carboplatin on progression-free survival in our study (HR, 0.72) is comparable with the AGO-OVAR 2.2/ICON 4 analyses (HR, 0.76).[5] Our study demonstrates also an improvement in progression-free survival that is maintained in patients whose platinum-free interval was less than 12 months and in patients who received first-line taxane therapy. This study clearly demonstrates that gemcitabine plus carboplatin is superior to carboplatin in terms of progression-free survival and response rate. Finally, relative to therapy with taxanes, gemcitabine plus carboplatin exhibited a preferable toxicity profile as evidenced by greatly diminished neuropathy and alopecia, which are of importance for the affected women. Therefore, gemcitabine plus carboplatin represents a new treatment option for patients with platinum-sensitive recurrent ovarian cancer.

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Authors' Disclosures of Potential Conflicts of Interest

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GLOSSARY

Cox proportional hazards model: The Cox proportional hazards model is a statistical model for regression analysis of censored survival data. It examines the relationship of censored survival distribution to one or more covariates. It produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

Febrile neutropenia: Symptoms include fever and a decrease in the number of neutrophils in the blood. A low neutrophil count increases the risk of infection.

GFR (glomerular filtration rate): GFR is the measure of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time. GFR is often used to determine renal function.

Thrombocytopenia: Reduced platelet count.

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